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08/635,130

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/635,130	04/19/96	CARAS	I P1001

18M1/0805

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EXAMINER	
DUFFY, P	
ART UNIT	**PAPER NUMBER**
1818	11

DATE MAILED: 08/05/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 6-12-97

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-39 is/are pending in the application.

Of the above, claim(s) 18-39 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1, 2, 5, 7, 8, 9, 10, 11, 14 and 16 is/are rejected.

☒ Claim(s) 3, 4, 6, 12, 13, 15 and 17 is/are objected to.

☒ Claims 1-39 are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

★ U.S GPO: 1996-409-290/40054

DETAILED ACTION

1. The preliminary amendment filed 7-11-96 has been entered into the record.

Election/Restriction

2. Claims 18-39 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected inventions. Election was made **without** traverse in Paper No. 10, mailed 6-12-97.

Sequence Compliance

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. For example, in Figure 4 recites the amino acid sequences for Lerk2 and Htk-L, but is not followed by a proper sequence identifier and is not separately listed the paper copy of the sequence listing. In addition, applicant is reminded that the claims must also comply by reciting the proper sequence identifiers. The sequences, not figures must be recited in the claims. Full compliance with the sequence rules is *required* in response to this office action. Failure to fully comply with the sequence requirements in the time period set forth in this office action will be held non-responsive.

Drawings

4. This application has been filed with informal drawings which are acceptable for examination purposes only. The drawings are objected to by the draftsperson under 37 C.F.R. 1.84 or 1.152. See PTO-948 for details. Correction of the noted defects can be deferred until the application is allowed by the examiner.

Specification

5. The title and abstract of the invention are not descriptive. A new title and abstract are required that is clearly indicative of the invention to which the *claims* are directed.

Claim Rejections - 35 U.S.C. § 112

6. Claims 1, 2, 5, 7, 8, 9, 10, 11, 14, and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses SEQ ID NO: 1 and 3 which corresponds to the nucleic acids sequence encoding the *human* species of protein AL-2 set forth as SEQ ID NO: 2 and 4. These SEQ ID NOs: 1-4 meet the written description and enablement provisions of 35 U.S.C. 112, first paragraph. However, the claim 10 is directed to or encompass sequences that hybridize to the isolated nucleic acids encoding SEQ ID NO: 2 or 4, and claims 1, 2, 5, 7, 8, 9, 10,11, 14, and 16 recite encoding nucleic acids which encompasses corresponding sequences from other species, sequence variants of the human species and derivatives that have a recited degree of identity.

None of these sequences meets the written description provision of 35 U.S.C. 112, first paragraph.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of isolated nucleotides encoding SEQ ID NO: 2 or 4 and full complements thereof, vectors comprising these nucleic acid sequences, host cells comprising the vectors and methods of using the host cells transformed with the vectors, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides (proteins) and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the human sequence.

Therefore, the only isolated nucleotides encoding SEQ ID NO:2 or 4, full complements thereof, vectors comprising these sequences, host cells transformed with the vectors and

methods of using the host cells comprising the vectors, but not the full breadth of the claim meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. (See page 1115.)

7. Claims 1, 2, 5, 7, 8, 9, 10, 11, 14, and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated nucleotides encoding SEQ ID NO: 2 or 4 and full complements thereof, vectors comprising these sequences, host cells transformed with the vectors and methods of using the host cells comprising the vectors, it does not reasonably provide enablement for corresponding sequences that have a recited degree of identity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The teachings of the specification are limited to the polynucleotides of SEQ ID NO:1 and 3 which code for the human AL-2 polypeptides set forth in SEQ ID NO: 2 and 4 respectively. The specification fails to teach how to make and use nucleotide sequences with at least 75% or 85% sequence identity to the amino acid sequences set forth in SEQ ID NO: 2 or 4. The specification fails to teach how to use variants which do not function identically to human AL-2. The claims are directed to isolated polynucleotides which encode a polypeptide having an amino acid sequence that is at least 75 or 85% identical to mature human AL-2 in SEQ ID NO:2 or 4, vectors containing the isolated polynucleotides, host cells transformed with the vector and methods of using the host cell to replicate the vector and produce the encoded protein. The claims reciting isolated nucleic acids encoded by a percent identity of the protein are non-enabling for the scope because the reference to the encoded protein merely by this limited

characteristic does not sufficiently define or enable the scope of either protein or the isolated nucleic acids which depend on the protein currently encompassed by the claims, especially in view of the fact that many tyrosine kinases and their corresponding ligands are closely related to this family of proteins (see sequence comparison of Lerk2, huHTKL, with AL-2 in Figure 4 and page 3, first full paragraph) and that the specification does not teach how to use proteins which not have biological activity. Applicants define AL-2 as an EPH-related tyrosine kinase ligand (page 4, lines 11-12). The name of the protein is arbitrarily assigned by the researcher who first isolates or clones it and does not serve to sufficiently define the physical or structural characteristics of the protein. Further, while many researchers name or designate the protein and nucleic acid encoding the protein because of a functional/biological activity that was observed, this is not sufficient because many proteins, especially in or related to the family of TK and cytokines, are pleiotropic in nature and posses some of the same or similar functional/biological properties as those associated with other distinct proteins even to the point of the same or similar assay being used to detect a particular activity. Thus, to define the isolated nucleotide by a percent protein homology does not serve to enable either the full scope of either the polynucleotide or protein. The specification is not enabled for isolated nucleic acids which encode sequence variants, mutants, homologs insertions or deletions as well as fusion proteins because the specification fails to teach a screening assay specific for AL-2 biological activity and the specification does not teach how to use variants without biological activity. These claims read on an infinite number of variations, substitutions, insertions and deletions of amino acid in the protein and the polynucleotide sequences. The specification fails to provide support for even a single amino acid change in either SEQ ID NO: 2 or 4, to support a variation in the isolated nucleic acid sequence. The specification fails to teach which amino acids are

critical to the identification of the biological activity and function of the protein, such that one skilled in the art would have sufficient guidance as to which amino acids could be potentially varied. In the absence of any structural/functional information, one of skill in the art, even in possession of a screening assay which solely identified AL-2 activity, would be reduced to randomly changing the DNA sequence to change amino acids to identify variants, mutants, etc. which have activity. However, as previously set forth, the screening methods using binding to an EPH-family receptor does not specifically identify the cytokine AL-2, much less identify related sequence variants, species variants, deletion and insertion mutants. Lerk2 and huHTKL are as applicant admits on page 7, lines 22-25 are also natural ligands for EPH-family tyrosine kinase receptors. Thus, an assay which detects binding to EPH-family tyrosine kinase receptors could not distinguish AL-2 from Lerk2 or huHTKL. Thus, a binding assay would not specifically detect sequence variants of AL-2 based on activity, to the exclusion of Lerk2 or huHTKL. There are no protein or DNA structure/function studies of record, and a general reference to making modified forms of the isolated DNA and protein and hence isolated polynucleotide encoding the protein variants is not seen to provide sufficient guidance for making modified versions of the isolated polynucleotide encoding the protein because the skilled artisan would not know where to start to make the various modifications, which base pairs to change to encode the protein variants, where to make changes and if the changes were in active regions, binding regions or other susceptible regions that would affect critical regions in the structure of the protein. Moreover, given that the mature form of AL-2 is 435 amino acids long, there would be a vast number of different amino acid and therefore polynucleotide sequences which could be postulated, given a recitation of at least 75% or 85% identical to the native AL-2. Given the vast number of possible sequences that could be encompassed, given the constraints posed by the

specification (i.e. a lack of an assay which specifically identifies AL-2 activity to the exclusion of other natural ligands) there is no enablement or guidance provided in the specification for insertions, deletions, variations, mutations could be made yield at least 75% or 85% identical to the native AL-2 of SEQ ID NO:2 or 4, and still produce a functional equivalent of AL-2. Further, in the absence of the specification setting forth regions that are critical for activity and binding, and in the absence of structure/function studies providing sufficient examples of possible variations encompassed by the 75% or 85% identical to the native AL-2 and further in the absence of sufficient guidance, it would constitute undue experimentation to enable the scope of the instant isolated nucleic acids encoding protein variants of at least 75% or 85% identical to the native AL-2. Without guidance from the specification as to exactly what variance could occur in the amino acid sequence, it would be undue experimentation for the skilled artisan to screen all possible variants especially in the absence of a screening assay which specifically detects AL-2 activity to the exclusion of other natural ligand to the EPH-family receptors. Because the disclosed screening assay would detect activity related cytokines, sequence variants of AL-2 could not be distinguished from other natural ligands. Thus, the skilled artisan would be required to conduct independent experiments to develop a screening assay specific for AL-2 activity and this activity would require independent thought, beyond which is taught in the specification.

The problem of predicting protein structure and function from nucleic acid and protein sequence data and in turn utilizing the sequence data to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in a given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain

positions in the sequence are critical to the protein' structure/function relationship, e.g. such as various sites or regions where the biological activity resides or regions directly involved in binding stability or catalysis; and in providing the correct three-dimensional spatial orientation for biologically active or binding sites, or for other sites which represent other characteristics/properties of the protein. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (Bowie et al., Science, 247:1306-1310,1990 see page 1306, column 2, paragraph 2; and Ngo et al., The Protein Folding Problem and Tertiary Structure Prediction, 1994 Merzer (ed.) pages 433 and 492-495; and Frommel et al., 1985). However, the specification has provided little or no guidance beyond the mere presentation of a nucleic acid encoding SEQ ID NO:2 or 4 in order to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the AL-2 protein which are tolerant to change (i.e. such as by amino acid substitutions, insertions or deletions) and the nature and extent of changes that can be made in the positions in order to obtain isolated nucleic acids that encode proteins that at least 75% or 85% identical to AL-2. Therefore, there is not adequate guidance for the vast number of mutants, variants, deletions and insertions that are encompassed by the claims, but is rather a mere invitation to the artisan to use the current invention as a starting point for further experimentation. The scope of the claims encompass modifications of the DNA encoding the protein that would be critical as well as non-critical for the biological activity of the protein. Thus, even if critical residues were identified or were able to be screened for, which in this case they are not, the mere identification of these critical regions would not be sufficient, as the skilled artisan would immediately recognize that the modified site must assume the proper three-dimensional configuration to be active-which conformation is in turn dependent on

surrounding residues. The substitution/insertion/deletion of non-essential residues can often unpredictably destroy activity. The art specifically teaches that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3):1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. The specification has not conceived any other functionally equivalent protein sequences, therefore it is deemed that to make each of the possible polynucleotide sequences encoding the amino acid modifications for each of the non-essential residues, even if only conservative replacements were made, would also constitute undue experimentation. The introduction of non-conservative substitutions, deletions or insertions further raises the possible number of species to be encoded by the isolated nucleic acid. Therefore, the specification has not presented enablement commensurate in scope with the claims.

In view of the lack of guidance in the specification as to which amino acids of AL-2 could be predictably varied, the unpredictability in the art regarding the effects of random and conservative changes to a proteins biological activity, the lack of an assay to specifically identify AL-2 activity, the lack of guidance in the specification as to amino acid residues which could be

varied in order to make isolated nucleic acids encoding the variants, one of skill in the art would be forced into undue experimentation to make and use isolated nucleic acids encoding a polypeptide having at least 75% or 85% identity with AL-2 of SEQ ID NO:2 or 4.

8. Claims 1, 2, 5, 7, 8, 9, 10, 11, 14, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claims 1, 2, 5, 7, 8, 9, 10, 11, 14, and 16 , the claims are indefinite because they fail to recite the particular means for determining sequence identity or homology to SEQ ID NO:2 or 4 as compared to the entire sequence or as compared to a fraction or to a specific portion of the sequence as described in the specification. As a result, the metes and bounds of the claims can not be determined.

As to claim 10, the claim is confusing because it defines "hybridizing" fragments, but depends from a claim encoding the protein. By definition a nucleotide which hybridizes is the non-coding strand. Thus it is completely unclear as to what applicants are claiming. Hybridizing (i.e. complementary DNA) or DNA encoding protein sequence variants. Correction is required.

Claim Rejections - 35 U.S.C. § 102 or 103

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

10. Claim 1 and 10 are rejected under 35 U.S.C. 102(a) as being anticipated by Hillier et al, the WashU-Merck EST Project, Accession H10006, NID g874828, on June 23, 1995.

Hillier et al teach an EST sequence which is an isolated nucleic acid which comprises 421 base pair matches within a sequence of 445 base pairs as compared to SEQ ID NO:1 and 3. Thus, the complement of this isolated nucleic acid would hybridize under stringent conditions to SEQ ID NO:1 and 3 and would inherently encode a protein that is antigenically cross-reactive to mature human AL2-s or AL2-l, absent convincing factual evidence to the contrary.

Claim Objections

11. Claims 1-17 are objected to as failing to comply with the sequence rules because the claims do not recite the proper sequence identifier as required by 37 CFR 1.821(d). Correction is required.

12. Claim 13 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 13 depends from claim 12. Claim 12 recites that the nucleotide sequence encodes the amino acid sequence for mature AL-2 shown in Figure 1A-1B or Figure 2A-2B. Claim 13 recites the same subject matter with no limitation of the selection of the sequence for Figure 1A-1B or Figure 2A-2B or further limitations and thus are deemed identical in scope and substantial duplicates. Correction is required.

13. Claims 3, 4, 6, 12, 13, 15 and 17 are objected to as depending from a rejected base claim.

Status of Claims

14. No claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 6:30 AM to 3:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached at (703) 308-4310.

Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application should be directed may be submitted to Group 1800 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The FAX number for Art Unit 1818 is (703) 308-4242.

Patricia A. Duffy, Ph.D.
August 1, 1997

Patricia A. Duffy

Patricia A. Duffy, Ph.D.
Patent Examiner
Group 1800